SYNOPSIS ESCITALDEP4002

Name of Sponsor/Company	Xian-Janssen Research & Development
Name of Finished Product	LEXAPRO®
Name of Active Ingredient(s)	JNJ-40518855-AFY (escitalopram)

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Prepared by: Xian-Janssen Research & Development

Protocol No.: ESCITALDEP4002 (LEX-CHN-IV-02)

Title of Study: Escitalopram in the Long-Term Treatment of Major Depressive Disorder With Associated Anxiety Symptom

NCT No.: NCT01814098

Clinical Registry No.: CR016381

Principal Investigator: Jiang Kaida, MD – Shanghai Mental Health Center, Shanghai, China.

Study Centers: The study was conducted at 13 sites in China.

Publication (Reference): None

Study Period: This study was conducted from 07 July 2009 (first subject enrolled) to 31 May 2011 (last subject out). The database lock was performed on 15 March 2013.

Phase of Development: 4

Objectives: To evaluate the efficacy and safety of long-term use of escitalopram in subjects with Major Depressive Disorder (MDD) with associated anxiety symptoms and to assess the effect of baseline degree of anxiety on treatment response.

Methodology: This was a 24-week, single-arm, open-label, multicenter, prospective, post-marketing study designed to evaluate the efficacy and safety of escitalopram (LEXAPRO) in subjects with a diagnosis of MDD with anxiety symptoms. Escitalopram was prescribed based on routine clinical practice. The initial dosage at baseline for all subjects was 10 mg/day. At the end of 2 weeks, the dose was to be adjusted (up to a maximum of 20 mg/day). In unresponsive subjects, a higher dose may have had been given for better efficacy based on the investigator's clinical judgment.

The study consisted of 9 visits (Visit 1 to 9). At baseline (Day 0 [Visit 1]), investigators were to check inclusion and exclusion criteria; obtain signed informed consent; collect demographic data, medical history, history of depression, previous anti-depression medications; evaluate and diagnose depression; and perform laboratory test results. Physical examination, vital signs (systolic and diastolic blood pressure, and pulse rate), body weight, Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton-Depression Rating scale (HAM-D-17), Hamilton Anxiety Scale (HAM-A), Clinical Global Impression (CGI) scales, and Short Form-12 (SF-12) Health Survey were to be recorded.

During the Treatment Period, all eligible subjects were to be followed-up for 24 weeks. Assessments of efficacy and safety were to be performed at Week 1 (Visit 2), Week 2 (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), Week 12 (Visit 6), Week 16 (Visit 7), Week 20 (Visit 8), and Week 24 (Visit 9). The total score of MADRS, HAM-D-17, HAM-A, and CGI scales was to be assessed at each visit, except CGI at Week 20 (Visit 8); while SF-12, an indicator of quality of life was to be evaluated at the baseline, Week 8 (Visit 5), and Week 24 (Visit 9).

Number of Subjects (planned and analyzed): Planned: Approximately 300 subjects with MDD with associated anxiety symptom were planned to be enrolled in this study.

Analyzed: A total of 318 subjects were screened in the study of which 302 subjects were included in the safety set (SS), 285 subjects were included in the full analysis set (FAS), and 187 subjects were included in the per protocol set (PPS).

Diagnosis and Main Criteria for Inclusion: Male or female subjects; age 18-65 years inclusive with a diagnosis of MDD with associated anxiety symptom according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria with a minimum baseline MADRS and HAM-A scores of 22 and 14, respectively were to be enrolled in the study.

Test Product, Dose and Mode of Administration, Batch No.: Subjects were administered escitalopram 10 mg tablets in 2 batches (2137620 [expiry date October 2010] and 2182918 [expiry date February 2012]).

Duration of Treatment: The duration of the treatment phase in this study was 24 weeks.

Criteria for Evaluation: Efficacy: This was measured by remission rate improvement using MADRS and HAM-A. Other rating scales included HAM-D-17, CGI (CGI-S [severity] and CGI-I [improvement]), and SF-12.

Safety: Safety and tolerability were evaluated throughout the study based on adverse event (AE) monitoring, vital signs (weight, pulse rate, and blood pressure), electrocardiogram (ECG), and laboratory tests (hematology, chemistry, and urine analysis).

Statistical Methods: Sample size determination: With an expectation of 70% remission rate for 24-week therapy of escitalopram and a clinical significant improvement of at least 5% of remission rate, a sample size of 238 subjects was required based on type I error rate of 0.05, a probability of type II error of 0.1, and power of 90%. Assuming a 25% dropout rate, a total of 300 subjects were planned to be enrolled in this study.

Efficacy analysis: Remission rate and its 95% confidence interval at the end of study were calculated. Statistical comparison was to be conducted between observed remission rate and prespecified value (namely 56%+5%=61%) with Z test. The 24-week therapy was to be considered superior to the traditional 8-week therapy when the p-value obtained was less than 0.05. For other efficacy variables, descriptive statistics were calculated to summarize the data. Paired-t test or signed rank sum test was used to detect the difference between post-therapy and baseline.

Subjects who received at least 1 dose of study drug and had at least 1 efficacy evaluation were included in the FAS. All subjects in the FAS who had good compliance (actual doses received between 80% and 120% of the total prescribed doses) without any major protocol violations, or missing primary efficacy endpoints were included in the PPS. The efficacy endpoints were analyzed for subjects in FAS and PPS. Full analysis set was the primary population of efficacy analysis and PPS was the secondary population of efficacy analysis.

Safety analysis: The safety set included subjects who received at least 1 dose of the study drug and had at least 1 safety assessment. Safety set was the primary population for safety analysis. All AEs were coded using the Medical Dictionary for Regulatory Activities, Version 15.1. All treatment-emergent adverse events (TEAEs) were to be analyzed. The percentage of subjects who had at least 1 recorded AE was to be calculated.

All laboratory test results were to be presented descriptively as well as in pre- versus post-treatment shift tables. Change from baseline was to be summarized using descriptive statistics. Frequency of clinically significant abnormal values was to be summarized. The ECG data were assessed as normal and abnormal based on investigator judgment and was to be presented in frequency table.

The changes of vital signs and weight from baseline at each visit were to be summarized using descriptive statistics.

Subgroup Analysis: Subgroup analysis was done for efficacy and AEs based on whether the dose of escitalopram was increased or not and subgroups were identified as the "non-dose elevation group" versus the "dose elevation group". Descriptive statistics were used for subgroup analysis.

For the primary efficacy analysis, subjects were divided into 3 subgroups based on MADRS total scores (≤22 to 29, 30 to 34, and ≥35) for baseline depression level; and based on HAM-A total scores (≤14 to 21, 22 to 29, and ≥30) for baseline anxiety level. Analyses were conducted in each subgroup.

Other subgroups analyses were based on 1) the subjects who had taken concomitant antipsychotic drug or not, 2) anti-depressant drugs taken within 30 days before enrollment or not, 3) per the number of episodes, and 4) concomitant use of tranquilizers or not.

RESULTS:

STUDY POPULATION:

Of the total 318 subjects screened in the study, 285 subjects were included in the FAS and 187 subjects were included in the PPS. Of the 302 subjects who were included in the SS, 200 (66.23%) completed the study. The most common reason for withdrawal was lost to follow-up and others (that included major protocol deviation and 'other' as mentioned in the case report form [CRF]).

A greater percentage of the population in the study was female. The mean (±standard deviation [SD]) age of subjects was 40.5 (±13.33) years and 41.3 (±13.49) years, in FAS and SS, respectively. The majority of subjects were married and lived with spouse. Approximately 60% of the subjects (each in FAS and SS) were educated at less than an undergraduate level (below middle school, middle school, or high school/secondary vocational school) and approximately 30% of the subjects (each in FAS and SS) were educated at a junior college and undergraduate level.

In the FAS and PPS, the total mean duration of depression was approximately 52 months (4 years, 4 months) and the mean current course of depression was approximately 9 months. The number of out-patient department visits during the last 6 months ranged from 0 to 18 (mean±SD: 1.6±2.48 in FAS and 1.8±2.54 in PPS). No major difference was seen in the percentage of subjects who had first-time diagnosis of depression and subjects who had repeat episodes of depression. The majority of the subjects had moderate disorder followed by severe disorder, and mild disorder. The majority of the subjects were able to perform activities of daily living independently.

EFFICACY RESULTS: Full analysis set was the primary population of efficacy analysis and PPS was the secondary population of efficacy analysis.

Primary Efficacy Analysis

Based on MADRS total score: In both FAS and PPS, a statistically significant difference was observed (p=0.0000) between the remission rate attained at 24-week treatment compared with 8-week treatment. Based on the results, the 24-week therapy was considered superior to the conventional 8-week therapy.

For the primary efficacy endpoint analysis, the remission rate at the end of Week 24 based on MADRS total scores was 73.33% for the FAS and 90.91% for the PPS. In the FAS, initially, the percentage of subjects who achieved remission was higher in "dose not increased" group till Week 4, which was considered statistically significant (p>0.05); however, thereafter till the end of study (Week 24), there was no significant difference in remission rates between the subgroups. The more severely ill subgroup (MADRS total score ≥35) took longer to achieve similar remission rates than the less severely ill subgroup (MADRS total score between 22 and 29). No major difference in remission rate was observed

between subjects who had received tranquilizers and those who had not received tranquilizers at Week 24 (72.06% versus 73.73%, respectively) in the FAS.

Based on HAM-A total scores: In the FAS, the overall remission rate of subjects with baseline HAM-A total scores between 14 and 21 was higher (79.03%) compared with subjects who had baseline HAM-A total scores between 22 and 29 (67.23%), and baseline HAM-A total scores ≥30 (76.92%).

Secondary Efficacy Analysis

The percentage of subjects in FAS that achieved greater than or equal to 50% decrease in MADRS total score from baseline at Week 24 was 87.37%. No major difference in response rates between the 2 subgroups was observed at Week 24 (85.84% in dose-not-increased compared with 88.37% for dose-increased).

Reduction of mean MADRS total scores at each visit compared with baseline was considered to be statistical significant ($p<0.0001$). The highest mean reduction in MADRS item scores was seen in reported sadness and apparent sadness (−3.3, each). This study had excluded subjects who had a score of 5 on item 10 (suicidal thoughts) of MADRS scale or had made a serious suicide attempt within the past 6 months; therefore, the baseline mean score of suicidal thoughts item was low (1.8). Despite a low baseline item score and lowest mean reduction (−1.6) at Week 24, the percentage of reduction in suicidal thought item was the highest compared with all other the items. Overall, approximately 80% reduction in the mean MADRS single-item scores was observed at Week 24, which was considered to be statistically significant ($p<0.0001$).

Reduction of mean HAM-A total scores at each visit compared with baseline was considered to be statistically significant ($p<0.0001$). The mean (±SD) baseline HAM-A somatic factor score was greater (16.7±3.66) than psychological factor score (11.0±4.68); however, the percentage reduction of mean scores of both factors was similar. At Week 24, the highest mean reduction in HAM-A single-item scores was observed in depression item (−2.4) and the lowest mean reduction was seen in genitourinary system symptoms (−0.9). Overall, approximately 80% reduction in the mean HAM-A single-item scores was observed at Week 24, which was considered to be statistically significant ($p<0.0001$).

The mean (±SD) baseline HAM-D-17 total score of 27.5 (±5.91) indicated a moderately to severely depressed population. At Week 24, the mean HAM-D-17 total score was 6.3 (±8.25), a decrease in 21.2 points from baseline, which was statistically significant ($p<0.0001$).

Approximately 80% of the total subjects were moderately ill to very seriously ill at Week 1; however, approximately 50% of the total subjects were considered normal, not ill; and approximately 35% of the total subjects were considered borderline or mildly ill at Week 24.

Approximately 50% of the total subjects slightly improved at Week 1 and approximately 90% of the subjects had overall improvement at Week 24 (very much improved in 57.75%, much improved in 18.66%, and minimally improved in 14.66%). There were no subjects with evident or significant aggravation of the condition.

At Week 24, the percentage of subjects who were “very satisfied” or “satisfied” was approximately 80%. A greater percentage of subjects were “very satisfied” in “dose-increased” group (43.02%) compared with “dose not increased” group (36.28%). A minimal percentage of subjects were “unsatisfied” and “very unsatisfied”.

The reduction of mean (±SD) somatic scores of SF-12 was greater in dose-increased group compared with dose-not increased group of subjects. The improvement in SF-12 somatic scores at Week 8 and Week 24 compared with baseline was statistically significant ($p<0.0001$) for both timepoints.

SAFETY RESULTS: All subjects who received at least 1 dose of the study drug with at least 1 safety evaluation were included in the SS. Of the 318 subjects who were screened, 302 (94.97%) subjects were included in the SS.

Of the overall 302 subjects, 80 (26.49%) subjects reported at least 1 TEAE during the 24-weeks treatment duration. There were no treatment-emergent deaths, 4 (1.32%) subjects experienced serious adverse events (SAEs) that lead to study drug discontinuation in 3 (0.99%) subjects, and 13 (4.30%) subjects experienced TEAEs that led to study drug discontinuation. All the SAEs were moderate to severe in intensity and reported to be cured. The majority (>50%) of the TEAEs that led to study drug discontinuation were moderate in intensity, possibly related. and reported to be cured.

The percentage of at least 1 TEAE in subjects who had their dose of escitalopram increased was slightly more (14.90%) compared with subjects in whom the dose was not increased (11.59%). The subjects who discontinued the study drug due to TEAEs were more in dose-not-increased group (2.98%) compared with dose increased group (1.32%).

The most common TEAEs by System Organ Class (SOC) (observed in ≥5% of the total subjects) were Gastrointestinal and Nervous system disorders (7.95%, each), and Psychiatric disorders (5.63%). The most frequently reported (observed in ≥2% of the total subjects) TEAEs by preferred term included headache (3.97%), nasopharyngitis (3.64%), nausea (2.98%), and dizziness (2.65%).

The majority of TEAEs and drug-related TEAEs reported in the study were mild to moderate in intensity. The majority of the TEAEs that occurred during the study were reported to be cured. Of the 82 (27.15%) subjects that experienced at least 1 drug-related TEAE by the investigator, 50 (16.56%) subjects and 32 (10.60%) subjects experienced at least 1 TEAE that were considered to be possibly-related and probably-related respectively by the investigator during the 24-week treatment period. The most frequently reported (observed in ≥2% of total subjects) drug-related TEAEs included headache and nausea (2.98%, each), and dizziness (2.32%).

The SOC with the highest percentage of TEAEs leading to study drug discontinuation were Psychiatric disorders and Nervous system disorders (1.32%, each). The incidence of any AE that led to study drug discontinuation was less than 1%.

No hematological or biochemical parameter was considered to be abnormal, clinically significant, except 1 instance each of leucocytes, glucose, and triglyceride. No abnormal clinically significant ECG was reported at baseline and Week 24.

No abnormal changes in heart rate, systolic blood pressure, and diastolic blood pressure findings were observed during the study, except 2 higher than normal values of heart rate observed at Week 24.

The mean (±SD) increase in body weight (kg) observed at Week 24 compared with baseline was 1.60 (±5.42) kg. The increase in body weight should be interpreted with caution as at the end of study, the values for 94 subjects were missing.

STUDY LIMITATIONS: Subjects with comorbid psychiatric disorders and those with high-risk tendency of suicide were excluded; hence, the population in this study may not be fully representative of patients with MDD. The causal relationship mentioned on the AE CRF page was not consistent with the protocol; however, this inconsistency had minimal impact on the overall safety results of the study.

CONCLUSIONS: The 24-week escitalopram therapy is superior compared with the conventional 8-week therapy. High remission rates were achieved and significant improvement in the symptoms of depression, anxiety, and overall quality of life of the subjects was observed as assessed on the MADRS, HAM-D-17, HAM-A, CGIs, and SF-12 scales.

Overall, escitalopram was effective and well-tolerated in the treatment of MDD associated with anxiety in Chinese study population. The results of this study support findings of previous studies with escitalopram.

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